ATTACHMENT 1

FDA'S HYPOTHETICAL

Company A[52] is currently marketing an approved drug product for intramuscular injection. Company B develops a device to deliver Company A's approved drug product for a different indication, to be delivered by a different method. No change in formulation to the drug product is needed.

Company B approached Company A to see if Company A would submit a supplemental new drug application to include the new indication and route of administration in the drug product labeling, but Company A refused. Company A also refused to provide a right of reference to data in its application.

Because Company B has been unable to obtain the cooperation of Company A, Company B approaches FDA and asks whether FDA would consider approving a device application stating that the device is intended to be used with drug product A delivered by the new route of administration for the new indication. Company B is willing to conduct all necessary studies to demonstrate that drug product A is safe and effective when delivered by the new route of administration by device B for the new indication.

The end user would obtain the device from Company B and the drug product from Company A. The drug product labeling would make no mention of device B, the new indication, or that the drug product can be delivered by the new route of administration.

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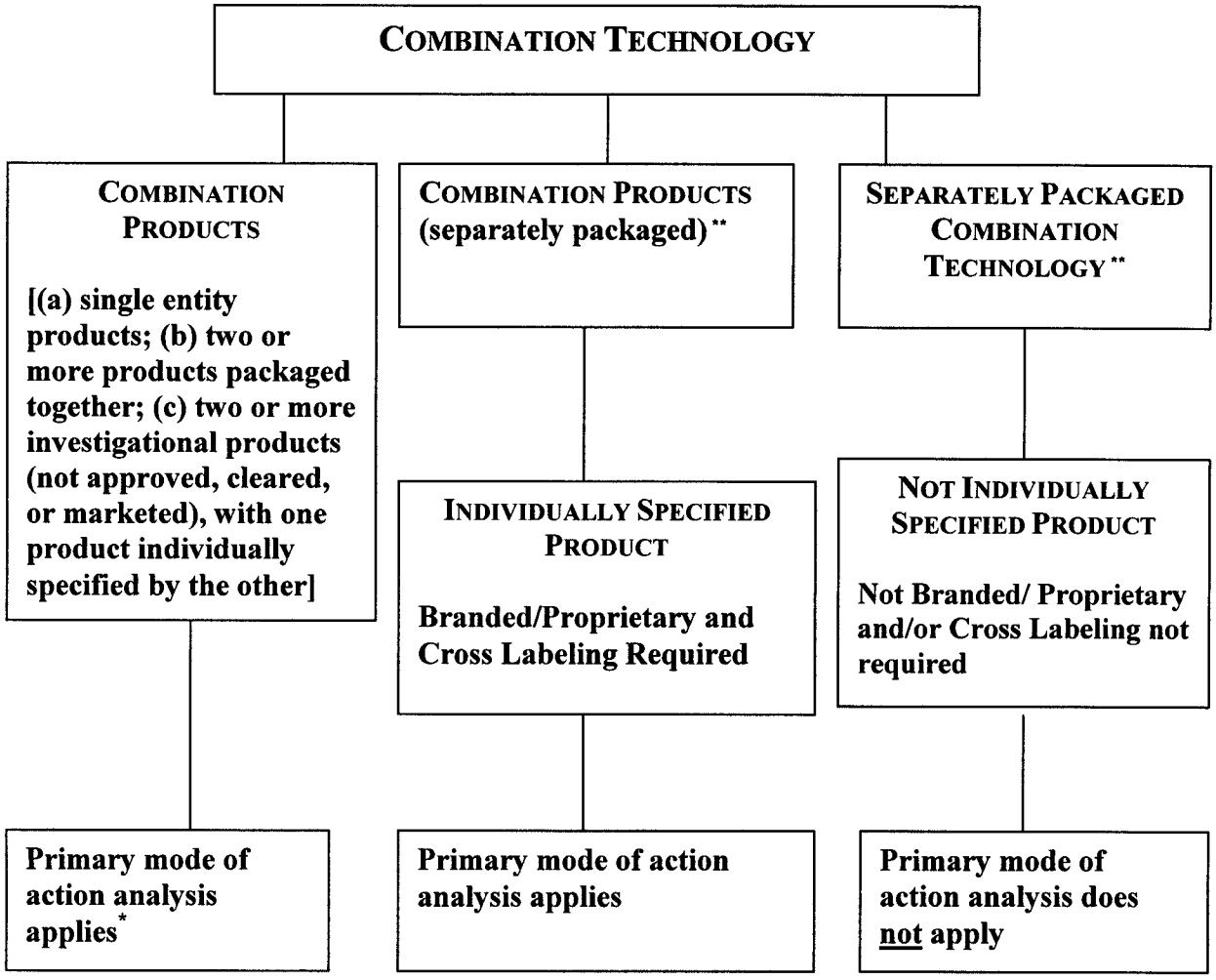
[52] As stated by FDA in its Federal Register notice, for reasons of convenience, this hypothetical refers to Company A as a manufacturer of an already approved drug and Company B as the sponsor of a device to be used with drug product A, 70 Fed. Reg. at 15634, n.3.

ATTACHMENT 2

PROPOSED DEFINITIONS

Important terms used in this submission and recommended for adoption by FDA, are presented graphically below, followed by proposed definitions. All terms in quotations have been defined. This flow chart also identifies those labeling concepts that are covered by this submission, and those that will be the subject of a subsequent set of comments.



* Labeling for this category of products not addressed by this submission.

** These technologies include two or more separately packaged products, where one of the products is an approved or cleared drug, device, or biological product.

- "Combination Technology" -- A technology comprised of two or more regulated products (e.g., a drug and device, biological product and device, or biological product and drug), where the regulated products are intended for use together. As contemplated by statutory authority, "combination products," as defined by 21 C.F.R. § 3.2, are a subset of this broader class of combinations.

- "Combination product" -- Those products defined at 21 C.F.R. § 3.2, as including:

  (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

  (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

  (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

  (4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect. 21 C.F.R. § 3.2.

- "Separately Packaged Combination Technology" -- A technology comprised of two or more separately packaged, regulated products (e.g., a drug and device, device and biological product, or biological and drug product), one of which is approved or cleared, which are to be used together, but that does not meet the regulatory definition of "combination product," because: (1) labeling of one regulated product does not "individually specify" the other regulated product; and/or (2) there is general consistency of indications, mode of delivery, and drug dosage/dosing schedule.

- "Cross-labeling" -- This term, which AdvaMed has chosen to use rather than "mutually conforming," is a particularly important definition, in that it provides the primary analysis for decisionmaking in this area. This definition sets forth the threshold analysis under Section 3.2(e)(3), as to whether labeling of two or more separately packaged products to be used together, must be conforming. Cross-labeling will be

triggered when: (1) a proposed product (i.e., device, drug, or biological product) intended for use with a separately marketed, approved or cleared product, "individually specifies" the other product in its labeling; and (2) upon approval or clearance of the proposed product, its labeling will not be generally consistent with the marketed, approved or cleared product's labeling, as further defined below.

When cross-labeling is triggered, both Company A and Company B must modify labeling (i.e., Company A will need to take steps to include information about the device in its labeling, while Company B will need to address the drug to be used with its device in its labeling). The separately packaged products will be considered a combination product, subject to primary mode of action analysis and related premarket review.

Conversely, cross-labeling will not be needed, when an approved product is not individually specified and/or there is "general consistency" of indications, mode of delivery, and drug dosage/dosing schedule. In this case, only Company B's labeling will need to address use of the drug and device together, and primary mode of action analysis will not apply.

- "Generally consistent labeling" -- Labeling of separately packaged products that generally conforms with respect to indications, mode of delivery, and drug dosage/dosing schedule. "Generally consistent" is intended to mean "similar" but not "identical" with respect to these parameters. Even if there are inconsistencies in these three parameters, labeling may nonetheless be considered generally consistent, if those inconsistencies can be addressed through a systematic risk analysis, as part of a risk management plan. Specifically, labeling will be "generally consistent," if: (a) the results of a risk assessment indicate that there are no issues with regard to safety and effectiveness that cannot be addressed in Company B's labeling; and/or (b) the risks can be adequately mitigated by Company B's risk management plan. In such cases, the differences can be resolved in the proposed device labeling. Similarly, "generally consistent" labeling does not require consistency of secondary aspects of drug labeling (e.g., precautions, warnings, preclinical data), assuming that safety and efficacy issues can be resolved in the proposed device labeling.

- "Individually Specified" product -- A regulated product (i.e., drug, device, or biological product) intended to be used with, or delivered by, another separately packaged, regulated product, that is named in that other product's labeling by its "branded/proprietary" name.

- "Not Individually Specified" product -- A regulated product (i.e., drug, device, or biological product) intended to be used with, or delivered by, another separately packaged, regulated product, that is not named in the other product's labeling by a "branded/proprietary" name. Examples include: generic drugs, other off-patent drugs

without market exclusivity, USP monograph drugs, drugs grandfathered by FDA, DESI drugs, OTC drugs, and broad categories of drugs specified only by therapeutic use or type.

- "Branded/Proprietary Product" -- A product that has a branded/trade name, and patent and/or non-patent market protection, and that is not a generic, USP monograph, DESI or OTC drug, or a drug grandfathered by FDA.